

A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland)

Rachael Z. Stolzenberg-Solomon^{1,2,*}, Pirjo Pietinen³, Philip R. Taylor⁴, Jarmo Virtamo³ & Demetrius Albanes¹
¹Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA; ²Division of Cancer Prevention, National Cancer Institute, Rockville, MD, USA; ³National Public Health Institute, Helsinki, Finland; ⁴Cancer Prevention Studies Branch, Center for Clinical Research, National Cancer Institute, Rockville, MD, USA

Received 21 June 2001; accepted in revised form 25 January 2002

Key words: anthropometry, medical conditions, metabolic syndrome, pancreatic cancer, physical activity, smokers.

Abstract

Objective: To examine the association between several medical conditions, anthropometric measurements, occupational and leisure physical activity, and pancreatic cancer in a cohort of male Finnish smokers.

Methods: We performed a cohort analysis of the 172 subjects who developed pancreatic cancer between 1985 and 1997 (median 10.2 years follow-up) among the 29,048 male smokers, 50–69 years old, who had complete baseline data and participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. Cox proportional hazards models were used to estimate multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CI).

Results: We observed positive associations between pancreatic cancer risk and self-reported history of diabetes mellitus (HR = 2.02, 95% CI 1.17–3.50) and bronchial asthma (HR = 2.16, 95% CI 1.17–3.98). Men having combined occupational and leisure activity greater than at sedentary levels had reduced risk for the cancer; for example those with moderate/heavy activity in both settings showed a HR of 0.42 (95% CI 0.22–0.83). There were no significant associations with other self-reported illnesses, total or HDL (high-density lipoprotein) cholesterol, height, weight, or body mass index.

Conclusions: Our data suggest that diabetes mellitus and bronchial asthma predict the subsequent risk of developing pancreatic cancer in male smokers, and that greater physical activity may reduce the risk.

Introduction

Although adenocarcinoma of the pancreas is a relatively uncommon cancer, it is a major source of cancer mortality, ranking fifth in the United States [1]. It is most often diagnosed at advanced stages, which contributes to its having among the lowest cancer survival rates [1]. Few risk factors have been identified, with cigarette smoke being the most consistent [1] and estimated to account for approximately 25% of the

incidence [2]. Several medical conditions have been associated with pancreatic cancer risk, with a positive association with diabetes mellitus being the best documented [3–5]. Both history of gallbladder disease (cholecystitis) and cholecystectomy have been associated with increased pancreatic cancer risk with the result for cholecystitis being more consistent than that for cholecystectomy [1]. There have also been less reliable findings for peptic ulcer disease being positively, and allergies inversely, associated with risk [1]. The metabolic syndrome associated with insulin resistance, characterized by hyperinsulinemia, low high-density lipoprotein cholesterol (HDL-C) levels, hypertension, and atherosclerosis, has been linked to obesity and lack of physical activity, and has paralleled the incidence of

* Address correspondence to: Rachael Stolzenberg-Solomon, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda MD 6120 Executive Blvd. MSC 7026, Rockville, MD 20852-7026, USA; E-mail: rs221z@nih.gov

some cancers (prostate, breast, colon) in Western populations [6] and could possibly be associated with pancreatic cancer considering its association with diabetes mellitus. Body mass index (BMI), a measure of obesity and predictor for type 2 diabetes, has been associated with pancreatic cancer [7–16], although inconsistently. Other studies have shown both positive and inverse associations between height and pancreatic cancer [8, 15, 17–19]. The purpose of this study is to examine the association between medical conditions, characteristics of the metabolic syndrome associated with insulin resistance, anthropometric measures, and physical activity with pancreatic cancer in a prospective cohort of male smokers.

Materials and methods

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a placebo-controlled, double-blind, 2×2 factorial design, primary prevention trial that tested the hypothesis of whether α -tocopherol or β -carotene reduced the incidence of lung cancer in male smokers [20]. Between 1985 and 1988, 29,133 eligible men, aged 50–69 years, in southwestern Finland, who smoked at least five cigarettes per day, were randomized to receive supplements (α -tocopherol 50 mg/day, β -carotene 20 mg/day, or both) or placebo. Exclusion criteria from the study included a history of malignancy other than nonmelanoma cancer of the skin or carcinoma *in situ*, severe angina on exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, receiving anticoagulant therapy, other medical problems which might limit long-term participation, or current use of supplements containing vitamin E (>20 mg/day), vitamin A ($>20,000$ IU/day), or β -carotene (>6 mg/day). The trial ended on 30 April 1993 and follow-up continued after randomization for the present study through November 1997 or until death, representing follow-up for up to 13 years (median 10.2 years). The study was approved by the institutional review boards of both the US National Cancer Institute and the National Public Health Institute in Finland, and all study participants provided written informed consent prior to the study's initiation. Details of the study rationale, design, and methods have been previously described [20].

Baseline characteristics, smoking and dietary factors

At their baseline visit the study participants completed questionnaires on general background characteristics including self-reported medical, smoking, and dietary

history, and had a venupuncture for blood after fasting 12 hours, from which serum total and HDL cholesterol were determined. Trained study staff using standard methods measured height, weight, and blood pressure. Blood pressure was measured in the right arm with a mercury sphygmomanometer and the lower of two measurements taken at least one minute apart was recorded. Body mass index was calculated from measured height and weight (kg/cm^2). Diet was assessed with a self-administered dietary history questionnaire, designed and validated specifically for the ATBC study, which determined the frequency of consumption and usual portion size of over 200 food items during the past year, using a color picture booklet as a guide for portion size [20]. Occupational activity was assessed by asking how much exercise and physical burden was experienced at work during the past year with examples such as: (i) “not working”, (ii) sedentary or “mainly sitting (*i.e.* watchmaker, radio mechanic, office work at desk)”, (iii) light or “walking quite a lot, but not lifting or carrying (*i.e.* foreman, shop assistant, light industrial work, office work where one has to move)”, (iv) moderate or “walk and lift a lot and often climb stairs or go up-hill (*i.e.* carpenter, tending cattle, work in engine shop, heavy industrial work)”, and (v) heavy physical work or “lift and carry heavy things, dig, shovel, or cut, etc. (forestry work, heavy farm work, heavy building and industrial work)”. Leisure-time activity was assessed by asking the average activity during the past year with examples such as: (i) sedentary or “reading, watching television, listening to radio, going to movies”, (ii) moderate or “walking, fishing, hunting, gardening regularly”, and (iii) heavy or “exercising to keep fit such as running, jogging, skiing, gymnastics, swimming, ball games, etc. fairly regularly”. For ten subjects with incomplete data on years smoked, we estimated years smoked by subtracting the subjects' age when they started smoking from their age at randomization.

Case ascertainment

Cases were ascertained from the Finnish Cancer Registry, which provides almost 100% case ascertainment in Finland [21, 22]. Two study physicians independently reviewed relevant medical records for reported incident pancreatic cancer cases [23]. Only cases confirmed by the study physicians as incident primary malignant neoplasm of the exocrine pancreas (ICD9-157) [24] were used for the present analysis. Eighty percent of these confirmed cases had histopathologic diagnosis assigned centrally by the study pathologists after examining pathology and cytology specimens [23]. As their etiology may be different from the exocrine tumors, islet cell

carcinomas (ICD9-157.4) [24] were excluded. There were 174 cases of confirmed exocrine pancreatic cancer of which 172 had complete blood pressure, height, weight, HDL and total cholesterol, and physical activity data at baseline.

Statistical analysis

Follow-up time for each participant was calculated from the date of randomization until diagnosis of pancreatic cancer, death, or November 1997, totaling 277,566 person-years of observation. Only those with complete baseline medical history, measured blood pressure, height, weight, HDL and total cholesterol, and physical activity data ($n = 29,048$) were included in the analyses. Variables examined for association with pancreatic cancer included self-reported medical history of gallstones, pancreatitis, peptic ulcer disease, diabetes mellitus, hypertension, coronary heart disease, allergic skin lesions, and bronchial asthma; serum total and HDL cholesterol; measured systolic and diastolic blood pressure; height, weight, and body mass index; and occupational and leisure activity. The variables were analyzed as continuous and categorical variables, with the latter based on the distribution in the cohort or commonly used cut-points (*i.e.* total and HDL cholesterol, high blood pressure). Trends across categories were tested using a calculated score variable and based on the median values of each category for the continuous variables. We defined the following based on current recommendations from the United States National Heart, Lung, and Blood Institute [25, 26]: measured high blood pressure as systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg, high serum cholesterol as ≥ 5.18 mmol/L (≥ 200 mg/dl), and low serum HDL cholesterol as ≤ 1.04 mmol/L (≤ 40 mg/dl). Because the proportion of heavy laborers (six cases, 9.2% of the population) and heavy leisure activity (nine cases, 6% of the population) were low, heavy labor was combined with the moderate occupational work activity group and the moderate and heavy leisure activity variables collapsed together to provide more stable risk estimates (Table 4). For assessing the combined effects of occupational and leisure activity, the two variables were cross-tabulated.

The distribution of the cases was compared to the non-cases using Wilcoxon rank sum, chi-square, and Fisher exact tests, for continuous and categorical variables, respectively. Hazards ratios (HR) and 95% confidence intervals (CI) were determined using proportional hazards models. Potential confounders were added to individual models in a stepwise fashion and were considered confounders if they were associated with both the disease and the risk factor ($p \leq 0.20$) and

changed the risk estimate $\geq 10\%$. Variables examined as potential confounders included age at randomization, smoking habits (years smoked, cigarettes smoked per day, pack-years); energy intake; energy-adjusted dietary folate, saturated fat, and carbohydrate intake; height, weight, and BMI; measured high blood pressure; history of diabetes mellitus and chronic bronchitis; occupational and leisure activity; and education. The dietary variables used to examine confounding were energy adjusted using the residual method described by Willett and Stampfer [27]. The analysis was initially restricted to those with complete dietary data (27,035 cohort subjects and 162 cases) to evaluate the dietary variables as potential confounders; however, the addition of these variables to models did not alter risk estimates, so the restriction was relaxed. Intervention and education were not included in models because neither was associated with pancreatic cancer. All multivariable models were adjusted for age at randomization, years smoked, cigarettes smoked per day, self-reported history of diabetes and bronchial asthma, occupational activity, and measured high blood pressure. The assumption of constant risk for proportional hazards models was tested with a time interaction term and lag analysis that excluded the first five years of observation. Effect modification between the anthropometric measures and energy, physical activity, history of diabetes mellitus, and smoking was tested through cross-product terms in the multivariable models and estimates of stratified HR. The combined effect of occupational and leisure activity was also examined. All statistical analysis was performed using Statistical Analysis Systems (SAS, Inc., Cary, North Carolina) software and statistical tests were two-tailed.

Results

Cases subjects were older, had lower energy intake, had smoked longer, were more likely to have a history of bronchial asthma or diabetes mellitus, to have high blood pressure as measured at baseline, and tended to be either non-working or have lower levels of occupational activity (Table 1).

Among self-reported health characteristics, histories of bronchial asthma and diabetes mellitus were significantly associated with pancreatic cancer in both crude and adjusted models (Table 2). Measured high blood pressure was also positively associated with the disease. Significant excess risk for preexisting bronchial asthma, diabetes, and measured high blood pressure was observed when cases diagnosed less than five years from baseline were excluded from the analysis (based on 98 cases, multivariate adjusted: bronchial asthma

Table 1. Baseline characteristics of pancreatic cancer case and non-case subjects, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Cohort (1985)

Characteristics	Medians (inter-quartile ranges) or proportions		
	Case subjects (n = 172)	Non-case subjects (n = 28,876)	p-Value ^a
Age, years	58 (55–62)	57 (53–61)	0.0001
Years smoked	40 (34–43)	36 (31–42)	0.002
Cigarettes per day	20 (15–25)	20 (15–25)	0.54
Pack-years	39 (26.5–50)	35 (24–46)	0.05
Energy intake, kcal/day	2609 (2204–3032)	2722 (2255–3263)	0.03
Height, cm	173 (169–179)	174 (169–178)	0.52
Weight, kg	79.1 (70.1–87.0)	78.3 (70.5–86.9)	0.93
Body mass index ^b	25.5 (23.7–28.0)	26.0 (23.7–28.5)	0.46
Self-reported health history			
Gallstones	5.2%	5.6%	0.86
Pancreatitis	2.3%	1.4%	0.32
Peptic ulcer disease	15.7%	17.5%	0.53
Allergic skin lesions	4.7%	7.4%	0.17
Bronchial asthma	6.4%	3.1%	0.01
Diabetes mellitus ^b	8.1%	4.2%	0.01
Hypertension ^b	14.5%	19.0%	0.14
Coronary heart disease	7.6%	7.5%	0.99
Clinical measurements			
Blood pressure, high ^{b,c}	69.8%	62.0%	0.04
Systolic blood pressure, mmHg ^b	142 (130–154)	140 (128–154)	0.75
Diastolic blood pressure, mmHg ^b	89 (80–94)	88 (80–94)	0.12
Total cholesterol, mmol/l ^{b,d}	6.25 (5.42–7.05)	6.15 (5.44–6.94)	0.55
HDL cholesterol, mmol/l ^{b,e}	1.14 (0.96–1.36)	1.14 (0.97–1.37)	0.85
Physical activity			
Occupational			
Sedentary (desk work)	14.5%	13.7%	
Light activity (walking)	14.5%	18.2%	
Moderate (walking and lifting)	14.5%	16.5%	
Heavy activity (heavy labor)	3.5%	9.2%	
Non-working	53.0%	42.2%	0.01
Leisure			
Sedentary (read, watch TV, go to movies)	44.8%	41.8%	
Moderate (walk, fish, hunt, gardening)	50.0%	52.2%	
Heavy (exercise to keep fit)	5.2%	6.0%	0.71

^a p-Value for Wilcoxon rank sum for continuous data, chi-square for categorical, and Fisher's exact test for pancreatitis.

^b Characteristic of the metabolic syndrome.

^c Systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg.

^d Conversion to mg/dl: cases, total cholesterol 241 (209–272) and non-cases, total cholesterol 237 (210–268); proportion with high total cholesterol (>5.18 mmol/L or 200 mg/dl) 80% cases and 82% non-cases.

^e Conversion to mg/dl: cases, HDL cholesterol 44 (37–54) and non-cases, HDL cholesterol 44 (37–53); proportion with low HDL cholesterol ≤ 1.04 mmol/L or ≤ 40 mg/dl, 34% cases and 35% non-cases.

HR = 2.68, 95% CI 1.24–5.81, diabetes mellitus HR = 2.23, 95% CI 1.08–4.60, and measured high blood pressure HR = 1.56, 95% CI 1.01–2.42). Preexisting diabetes continued to be significantly associated with pancreatic cancer even after the exclusion of cases developing within 8 years of baseline (n = 48 cases: HR = 3.09, 95% CI 1.22–7.82), while bronchial asthma and measured high blood pressure risk estimates were attenuated. The other self-reported health-related

characteristics were not associated with pancreatic cancer.

No association was observed with pancreatic cancer and weight, height, BMI, diastolic blood pressure, and total and HDL cholesterol (Table 3) and the lack of association remained when the cases that occurred during the first five years of follow-up were excluded (based on 98 cases, multivariate, fifth compared to first quintile: weight, additional adjusted for height, HR =

Table 2. Adjusted hazard ratios and 95% confidence intervals for pancreatic cancer according to health history, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Cohort, randomization through November, 1997

Characteristic	Cases, n	Person-years	Age-adjusted model: HR (95% CI)	Multivariate-adjusted model ^a : HR (95% CI)
<i>Self-reported health history</i>				
Gallstones				
No	163	262,176	1.00 (reference)	1.00 (reference)
Yes	9	15,389	0.88 (0.45–1.71)	0.84 (0.43–1.65)
Pancreatitis				
No	168	273,767	1.00	1.00
Yes	4	3,799	1.81 (0.67–4.89)	1.50 (0.55–4.07)
Peptic ulcer disease				
No	145	229,521	1.00	1.00
Yes	27	48,045	0.85 (0.56–1.28)	0.85 (0.56–1.28)
Allergic skin lesions				
No	164	257,114	1.00	1.00
Yes	8	20,451	0.63 (0.31–1.28)	0.59 (0.29–1.20)
Bronchial asthma				
No	161	269,775	1.00	1.00
Yes	11	7,790	2.23 (1.21–4.11)	2.16 (1.17–3.98)
Diabetes mellitus ^b				
No	158	266,896	1.00	1.00
Yes	14	10,669	2.17 (1.26–3.76)	2.02 (1.17–3.50)
Hypertension ^b				
No	147	226,987	1.00	1.00
Yes	25	50,579	0.77 (0.50–1.18)	0.70 (0.46–1.09)
Coronary heart disease				
No	159	258,528	1.00	1.00
Yes	13	19,037	0.99 (0.56–1.74)	0.91 (0.51–1.61)
<i>Clinical measurements</i>				
Blood pressure, high ^{b,c}				
No	52	107,805	1.00	1.00
Yes	120	169,761	1.38 (1.00–1.92)	1.36 (0.98–1.89)
Total cholesterol, high ^{b,d}				
No	34	47,465	1.00	1.00
Yes	138	230,101	0.85 (0.59–1.24)	0.88 (0.60–1.28)
HDL cholesterol, low ^{b,e}				
No	113	181,116	1.00	1.00
Yes	59	96,449	0.98 (0.72–1.35)	0.94 (0.68–1.29)

^a All models adjusted for age, years smoked, total number of cigarettes smoked per day, self-reported history of diabetes and bronchial asthma, occupational activity, measured high blood pressure.

^b Characteristic of the metabolic syndrome.

^c Measured high blood pressure defined as systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg.

^d High total cholesterol defined as ≥ 5.18 mmol/L (≥ 200 mg/dl).

^e Low HDL cholesterol defined as ≤ 1.04 mmol/L (≤ 40 mg/dl).

0.73, 95% CI 0.36–1.49, p -trend = 0.44; height HR = 1.67, 95% CI 0.88–3.18, p -trend = 0.10; BMI HR = 0.90, 95% CI 0.45–1.77, p -trend = 0.30; diastolic blood pressure HR = 0.96, 95% CI 0.51–1.81, p -trend = 0.78; total cholesterol HR = 1.02, 95% CI 0.56–1.86, p -trend = 0.61; and HDL cholesterol HR = 0.97, 95% CI 0.53–1.76, p -trend = 0.99). There was also a suggestion of an increasing trend for pancreatic cancer with greater systolic blood pressure up to the fourth quintile with the risk attenuated at above 157 mmHg (Table 3), and the same risk pattern re-

mained with the 5-year lag analysis (compared to first quintile, fourth quintile HR = 2.57, 95% CI 1.32–5.00).

There were non-significant inverse associations between greater occupational and leisure activity and pancreatic cancer (Table 4). All risk estimates were proportional over time and the inverse association with greater occupational activity remained the same after the exclusion of the cases prior to the first 5 years ($n = 98$ cases; multivariable adjusted, compared to sedentary, moderate HR = 0.71, 95% CI 0.36–1.40, heavy

Table 3. Adjusted hazards ratios and 95% confidence intervals for pancreatic cancer according to anthropometric and biologic measure quintiles, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Cohort, randomization through November 1997

Characteristic	Hazards ratios (95% confidence intervals)					<i>p</i> -Trend
	Quintile					
	1 (reference)	2	3	4	5	
Height, cm	≤168	>168 and ≤171	>171 and ≤175	>175 and ≤178	>178	
Cases, n	37	22	45	23	45	
Person-years	54,558	47,133	70,641	45,330	59,904	
Age-adjusted	1.00	0.72 (0.43–1.22)	1.00 (0.65–1.55)	0.82 (0.49–1.39)	1.28 (0.83–1.98)	0.21
Multivariate-adjusted ^a	1.00	0.72 (0.43–1.22)	1.01 (0.65–1.56)	0.82 (0.49–1.39)	1.28 (0.82–1.98)	0.22
Weight, kg ^b	≤68.5	>68.5 and ≤ 75.2	>75.2 and ≤81.3	>81.3 and ≤89.2	>89.2	
Cases, n	37	29	32	42	32	
Person-years	54,552	55,428	56,166	56,070	55,349	
Age-adjusted	1.00	0.80 (0.50–1.32)	0.89 (0.56–1.44)	1.20 (0.77–1.87)	0.97 (0.60–1.56)	0.62
Multivariate-adjusted ^{a,c}	1.00	0.77 (0.47–1.26)	0.80 (0.49–1.30)	1.01 (0.63–1.62)	0.73 (0.42–1.23)	0.46
BMI, kg/m ² ^b	≤23.1	>23.1 and ≤25.1	>25.1 and ≤26.9	>26.9 and ≤29.2	>29.2	
Cases, n	34	40	40	24	34	
Person-years	54,721	56,128	56,155	56,037	54,525	
Age-adjusted	1.00	1.18 (0.75–1.87)	1.19 (0.75–1.88)	0.72 (0.43–1.22)	1.07 (0.67–1.73)	0.67
Multivariate-adjusted ^a	1.00	1.18 (0.74–1.86)	1.15 (0.72–1.81)	0.67 (0.39–1.13)	0.91 (0.56–1.48)	0.24
Multivariate-adjusted ^{ad}	0.85 (0.54–1.34)	1.00 (reference)	0.97 (0.63–1.51)	0.57 (0.34–0.94)	0.77 (0.48–1.23)	
Systolic blood pressure, mmHg ^b	<125	≥125 and <135	≥135 and <144	≥144 and <158	≥158	
Cases, n	22	33	39	52	26	
Person-years	55,428	56,569	59,316	56,052	50,201	
Age-adjusted	1.00	1.42 (0.83–2.44)	1.55 (0.92–2.62)	2.10 (1.27–3.47)	1.11 (0.62–1.97)	0.52
Multivariate-adjusted ^a	1.00	1.41 (0.82–2.42)	1.54 (0.91–2.60)	2.06 (1.25–3.41)	1.07 (0.60–1.90)	0.62
Diastolic, blood pressure mmHg ^b	<78	≥78 and <84	≥84 and <89	≥89 and <96	≥96	
Cases, n	36	33	17	56	30	
Person-years	55,680	59,307	40,169	70,391	52,018	
Age-adjusted	1.00	0.89 (0.55–1.42)	0.69 (0.39–1.22)	1.29 (0.85–1.97)	0.95 (0.59–1.55)	0.65
Multivariate-adjusted ^a	1.00	0.90 (0.56–1.44)	0.68 (0.39–1.21)	1.30 (0.85–1.97)	0.95 (0.59–1.55)	0.68
Total cholesterol, mg/dl ^b	<203	≥203 and <227	≥227 and <249	≥249 and <276	>276	
Cases, n	37	28	31	35	41	
Person-years	53,990	55,447	56,065	55,621	56,442	
Age-adjusted	1.00	0.75 (0.46–1.22)	0.83 (0.51–1.33)	0.93 (0.59–1.48)	1.09 (0.70–1.70)	0.44
Multivariate-adjusted ^a	1.00	0.76 (0.47–1.25)	0.85 (0.53–1.37)	0.96 (0.61–1.52)	1.13 (0.72–1.76)	0.36
HDL cholesterol, mg/dl ^b	<36	≥36 and <41.7	≥41.7 and <47.1	≥47.1 and <55.2	>55.2	
Cases, n	39	24	49	21	39	
Person-years	54,586	55,707	55,961	56,576	54,736	
Age-adjusted	1.00	0.60 (0.36–1.00)	1.21 (0.79–1.84)	0.52 (0.30–0.88)	0.99 (0.64–1.54)	0.96
Multivariate-adjusted ^a	1.00	0.63 (0.38–1.05)	1.30 (0.85–1.98)	0.56 (0.33–0.96)	1.05 (0.67–1.65)	0.83

^a All models adjusted for age, years smoked, total number of cigarettes smoked per day, self-reported history of diabetes and bronchial asthma, occupational activity, measured high blood pressure.

^b Characteristic of the metabolic syndrome.

^c Additionally adjusted for height.

^d Alternate reference category.

HR = 0.63, 95% CI 0.33–1.22, *p*-trend = 0.19). For activity categories not collapsed, a significant protective association was observed for the heavy labor alone (compared to sedentary, multivariate adjusted: walking HR = 0.78, 95% CI 0.45–1.35; walking with lifting HR = 0.87, 95% CI 0.50–1.52; heavy labor HR = 0.27, 95% CI 0.15–0.89; *p*-trend = 0.07; non-workers

HR = 0.97, 95% CI 0.60–1.57) and no association observed for leisure activity (compared to sedentary, multivariate adjusted: walking HR = 0.90, 95% CI 0.66–1.23; exercise HR = 0.86, 95% CI 0.43–1.72, *p*-trend = 0.48). Compared to those with both sedentary occupational and leisure activity (Table 4), all levels of activity greater than sedentary showed protective associations. Inverse but

Table 4. Adjusted hazards ratios (HR) and 95% confidence interval (CI) for pancreatic cancer of occupational and leisure time physical activity, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Cohort, randomization through November, 1997^a

Work activity		Leisure activity		<i>p</i> -Trend
		Sedentary	Moderate/heavy	
		77/113,697 1.00 (reference)	95/163,869 0.88 (0.65–1.20)	0.43
Cases, n/person-years	25/40,087	18/18,027	7/22,059	
Sedentary, HR (95% CI)	1.00 (reference)	1.00 (reference)	0.34 (0.14–0.81)	0.02
Cases, n/person-years	25/53,391	10/20,222	15/33,169	
Light, HR (95% CI)	0.77 (0.45–1.35)	0.51 (0.23–1.10)	0.50 (0.25–0.99)	0.92
Cases, n/person-years	31/74,026	15/32,980	16/41,046	
Moderate/heavy, HR (95% CI)	0.69 (0.41–1.17)	0.42 (0.22–0.93)	0.42 (0.22–0.83)	0.87
<i>p</i> -Trend	0.20	0.04	0.68	
Cases, n/person-years	91/110,062	34/42,468	57/67,594	
Not work, HR (95% CI)	0.98 (0.60–1.58)	0.59 (0.32–1.08)	0.66 (0.37–1.16)	0.61

^a All models adjusted for age, years smoked, total number of cigarettes smoked per day, self-reported history of diabetes and bronchial asthma, and measured high blood pressure.

non-significant associations were also observed for non-workers in both leisure activity strata.

There were no significant interactions between the anthropometric measures and energy, smoking habits, physical activity, or history of diabetes mellitus, with the exception of height and energy such that compared to those with low energy intake (≤ 2419 kcal/day) and short stature (≤ 170 cm), those who were tall (> 176 cm) and had low energy intake had a significant increased risk of pancreatic cancer (multivariate adjusted: HR = 2.19, 95% CI 1.28–3.74, *p*-interaction = 0.05) and height and cigarettes smoked per day such that, compared to those who smoked a low number of cigarettes per day (≤ 15 cigarettes/day) and had short stature (≤ 170 cm), those who were tall (> 176 cm) and smoked a high number of cigarettes per day had a non-significant increased risk of pancreatic cancer (multivariate adjusted: HR = 2.18, 95% CI 0.93–5.13, *p*-interaction = 0.02).

Of all the covariates assessed, only age at randomization altered most risk estimates and height confounded the risk estimate for weight. All risk estimates for the factors examined were statistically proportional over time (*p*-value > 0.05).

Discussion

We observed a positive association for self-reported preexisting diabetes mellitus, which remained after excluding early cases. It has been difficult to disentangle whether diabetics are truly at elevated risk for pancre-

atic cancer or if the condition is related to subclinical pancreatic cancer. Pancreatic cancer can induce peripheral insulin resistance and diabetes [20, 28], which disappears after tumor resection [29]. Several other prospective studies have also shown positive associations between self-reported diabetes and pancreatic cancer [3, 4, 10, 14, 30, 31]. The association with diabetes often remained among those studies with long follow-up (*i.e.* > 5 and > 10 years) [3, 10, 32]; however, attenuation over time has also been observed [4, 30, 31]. As diabetes is under-diagnosed and self-reported diabetes likely under-represents its true prevalence, a recent cohort study with an average 25 years of follow-up found a significant doubling of risk (relative risk (RR) = 2.15, 95% CI 1.22–3.80, *p*-trend = 0.01) associated with elevated post-load plasma glucose levels [9]. Of interest, cigarette smoke appears to influence glucose and lipid levels, as well as the incidence of type 2 diabetes, independent of body composition [33–35]. Although the latency of pancreatic cancer is unknown, our findings and those of others suggest that diabetes and glucose intolerance predict pancreatic cancer over an extended period of time.

Weight and BMI, important risk factors for type 2 diabetes, have also been positively associated with pancreatic cancer, although not consistently [7, 8, 11, 19] and several prospective studies suggest that BMI may be associated with pancreatic cancer [9, 10, 12–15]. In a large case-control study conducted within a retrospective home maintenance organization cohort having 24 years of follow-up (average ~ 12 years), Friedman and Van den Eeden [10] found modest

positive associations for both weight and BMI with pancreatic cancer (per 5 kg weight increase: $RR = 1.06$, 95% CI 1.01–1.11 and BMI per unit increase: $RR = 1.02$, 95% CI 1.00–1.04). In the previously mentioned post-load plasma glucose study an elevated risk was observed for BMI with pancreatic cancer in men (lowest to highest quartile BMI: $RR = 3.07$, 95% CI 1.53–6.15, p -trend = 0.001) with no association among women (lowest to highest quartile BMI: $RR = 0.75$, 95% CI 0.32–1.95, p -trend = 0.95). A large cohort study of American Cancer Society volunteers showed weak but significant positive associations [14], and a pooled analysis of the Nurses Health and Health Professional Follow-up Study cohorts showed significant positive associations [15] for pancreatic cancer among both men and women with BMI > 30 kg/m² compared to those with normal weight. BMI and weight were unrelated to pancreatic cancer in the present study of smokers. Smokers tend to have lower BMI and body weight than non-smokers [36, 37] even after controlling for dietary intake, physical activity, age, and education [38, 39], and nicotine is known to increase metabolic rate and energy expenditure both at rest and during activity [40]. Despite these facts the majority of our population was overweight (BMI > 25 kg/m²) with a distribution of BMI similar to other populations that have observed positive associations with pancreatic cancer [14, 15]. Smokers also tend to be less well nourished than non-smokers as a result of poor diets and the anti-nutrient effects of cigarette smoke [39, 41], although neither dietary intake nor smoking habits altered the lack of association that we observe with BMI. Considering the potential influence of smoking on body weight and nutritional status, effect modification by smoking status on the association of body weight and pancreatic cancer should be explored in populations that include non-smokers.

We observed a suggestion of a positive association with elevated measured blood pressure at baseline, particularly systolic blood pressure, although self-reported history of hypertension was not related to pancreatic cancer in the present analysis. One other prospective study observed associations with diastolic and systolic blood pressure of 9% and 5% per 10 mmHg, respectively [10]. Our observed attenuation of the association with systolic blood pressure in the highest quintile (≥ 158 mmHg) could possibly be explained by subsequent treatment for hypertension for subjects in this quintile during follow-up. It has been hypothesized that insulin resistance and obesity-related hyperinsulinemia may enhance sodium retention and stimulate the sympathetic nervous system, thereby contributing to hypertension [42]. Hyperinsulinemia in patients with insulinoma, however, is associated with

neither insulin resistance nor hypertension [43–47]. Further, evidence exists for a local renin–angiotensin system in the pancreas [48]; whether it is related to the observed association for blood pressure and pancreatic cancer is unknown. We did not observe associations with other clinical factors related to insulin resistance, such as obesity and low HDL cholesterol. In addition, we used blood pressure as measured at baseline and misclassification could occur, thus influencing risk estimates. Therefore, it is possible that the associations between blood pressure and pancreatic cancer in our study and that of Friedman and Van den Eeden [10] are due to chance.

A non-significant protective association was also observed for greater occupational and leisure physical activity, particularly among those employed at baseline, which was independent of smoking, BMI, and energy intake and became significant with occupational and leisure activity stratification, despite its relatively crude assessment. Our finding is also supported by a pooled prospective analysis of the Health Professionals Follow-up Study and the Nurses Health Study ($n = 323$ cases) that showed a statistically significant inverse association between moderate leisure activity (less than six metabolic equivalents) and pancreatic cancer risk (pooled multivariate-adjusted highest quintile compared to lowest: $RR = 0.45$, 95% CI 0.29–0.70, p -trend < 0.001) [15], as well as a population-based case-control study ($n = 312$ cases, $n = 2919$ controls) that observed a significant inverse association in the highest quartile of a composite moderate and strenuous physical activity index in men (multivariate-adjusted $OR = 0.53$, 95% CI 0.31–0.90, p -trend = 0.04) but not in women (multivariate-adjusted $OR = 0.80$, 95% CI 0.41–1.54, p -trend = 0.35) [16]. Other prospective cohort studies have not demonstrated a relationship between physical activity and pancreatic cancer [49, 50]. The only animal experiment to examine exercise and pancreatic cancer showed that, in azaserine-treated rats that were subsequently exercised, early-life physical activity suppressed, while later life exercise enhanced, the development of preneoplastic pancreatic acinar cell lesions compared to sedentary animals [51]. The mechanisms that explain our observed associations with physical activity and diabetes are independent of obesity and energy intake and could possibly be related to insulin; for example physical activity decreases fasting insulin and type 2 diabetes is associated with insulin resistance [52]. Insulin is a known mitogen for tumor growth [52].

Among other self-reported medical conditions only a history of bronchial asthma was associated with increased risk of pancreatic cancer. A similar association has been observed in a prospective study of World War

II veterans with 29 years of follow-up [53]. Bronchial asthma may be a marker for cigarette dose; however, adjustment for smoking did not alter the risk estimates, and lung emphysema (multivariate-adjusted HR = 0.91, 95% CI 0.51–1.63) and chronic bronchitis (multivariate-adjusted HR = 0.86, 95% CI 0.49–1.52), which may similarly be disease markers of cigarette exposure, were not associated with pancreatic cancer. The low prevalence of the medical conditions examined (e.g. pancreatitis) and the likelihood of misclassification of self-reported disease (e.g. peptic ulcers, gallstone disease, coronary heart disease, hypertension) could both attenuate power and risk estimates. For example, subjects who have *Helicobacter pylori* carriage are often asymptomatic without dyspeptic symptoms [54, 55] and hypertension is known to be under-diagnosed and sub-optimally treated [56]. In addition, individuals who report these often-under-diagnosed diseases (e.g. peptic ulcers, gallstone disease, coronary heart disease, hypertension) may have unmeasured characteristics (e.g. healthier habits) that may explain the non-significant inverse association we observed between these conditions and pancreatic cancer.

In conclusion, our data suggest that diabetes mellitus and bronchial asthma predict subsequent risk of developing pancreatic cancer in male smokers, and that greater physical activity may reduce risk. There was a suggestion of a positive association with measured high blood pressure, and other self-reported illnesses, total and HDL cholesterol, height, weight, and body mass index were unrelated to the disease. A potential limitation to our study is that lack of exposure assessment during follow-up could contribute to misclassification and attenuated risk estimates; however, the fact that our risk estimates were proportional over time argues against this. Although some of our findings may not be generalizable to non-smoker populations, because smokers have a greater risk for pancreatic cancer, many of our findings confirm results from non-smoking populations [1, 4, 10, 14, 30, 31] and may provide clues to mechanisms. The strength of our study is its large prospective nature, which eliminates recall and reverse causation bias. Identifying potentially modifiable factors that may reduce the burden of pancreatic cancer has important public health implications, particularly in the high-risk smoker population.

Acknowledgement

This research is supported by the US Public Health Service contracts N01CN45165 and N01CN45035 from the National Cancer Institute.

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